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Reduction of Cognitive Decline in Patients with or at High Risk for Diabetes

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Abstract

Purpose of review—The incidence of Alzheimer's disease and related disorders is expected to triple by 2050. People with type 2 diabetes and prediabetes have a higher risk of cognitive dysfunction, including Alzheimer's disease and vascular dementia. Controversy remains about when and how to prevent and treat cognitive dysfunction in people with or at high risk of diabetes.

Recent findings—In our review of ongoing clinical trials, we have found that there has been an increase in the number of studies assessing the efficacy of pharmacological and non-pharmacological approaches to prevent or slow down cognitive impairment among people with or at high risk of diabetes.

Summary—Despite the considerable risk of cognitive impairment in people with diabetes and prediabetes, there is not enough evidence to support a specific treatment to prevent or slow mild cognitive impairment, or progression to Alzheimer's disease or related disorders. Several ongoing trials are attempting to identify the usefulness of several compounds, as well as lifestyle changes including exercise and diet. Direct mechanisms linking diabetes to cognitive decline have not been elucidated.

Keywords

Alzheimer's Disease; Dementia; Mild Cognitive Impairment; Clinical Trials; Insulin; Prediabetes

Introduction

The number of people worldwide living with dementia will double almost every 20 years, reaching 74.7 million in 2030 and 131.5 million in 2050 [1]. It is estimated that worldwide, approximately 2% (825,000) cases of Alzheimer's disease (AD) – the main cause of age-related dementia – are currently attributable to diabetes, including 3% (nearly 175,000) in the US [2]. Of considerable concern is the large and rapidly growing number of older adults

who have prediabetes, a metabolic condition associated with obesity that significantly increases the risk of developing type 2 diabetes [3]. In the U.S., for example, nearly 50% of adults have diabetes or pre-diabetes [4], suggesting that there is a substantial population that may have a dual risk of developing both diabetes and cognitive decline [5].

Evidence associating type 2 diabetes and severe cognitive decline emerged from epidemiological studies [6, 7]. The clinical and molecular determinants whereby diabetes increases the risk of cognitive impairment and AD remain to be elucidated. However, dysregulation of insulin might be directly linked to the increased vulnerability of people with or at high risk of type 2 diabetes. The role of insulin in the brain continues to be mysterious. Before the work of Chowers, Lavy and Halpern [8] demonstrated that insulin promoted the uptake of glucose by the brain, it was believed that the brain was insensitive to insulin. However, insulin receptors in the brain [9] were in fact found to be enriched in the olfactory areas and associated limbic regions[10], areas of pivotal importance for cognition and mood. Since then, the notion that insensitivity to insulin in the brain would lead to 'diabetes of the brain' [11], which would manifest as cognitive dysfunction, has emerged. Epidemiological studies have shown that Alzheimer's disease is exceedingly common among people suffering type 2 diabetes [16]. It has been reported that intranasal administration of insulin in small groups of adults with mild cognitive impairment (MCI) or AD has been associated with improvement of memory [12, 13], structural brain changes, and cerebral spinal fluid (CSF) [14] markers of AD pathology. Interestingly, this effect is more evident with short-term insulin and among individuals who do not carry allele 4 of the apolipoprotein E (APOE). In addition, administration of metformin – a medication that improves glucose control and helps reduce hyperinsulinemia – to a small group of elderly individuals who are overweight or obese (without treated diabetes) or who have MCI, over a period of 12 months, was associated with improvements in memory [15]. However, the prevention, prognosis, and management of cognitive decline associated with diabetes and prediabetes remain uncertain.

Cognitive Decline in Patients with or at High Risk of Diabetes

Cognitive performance in neuropsychological tests of Individuals with type 2 diabetes is lower than people of their same age, sex and education, across all ages and beginning in the very early stages of dysglicemia [17, 18]. Not all cognitive domains are affected equally: verbal memory, information processing speed, attention, and executive functioning are particularly affected [19]. The magnitude of these changes varies from subtle to mild cognitive impairment and dementia [20]. Determinants of the type of impairment, speed of decline, and progression to either Alzheimer's disease or vascular dementia, are not known. In individuals with controlled type 2 diabetes, insulin-related variables (i.e. fasting insulin, C-peptide, and the Homeostasis Model Assessment of Insulin Resistance (HOMA2-IR)) are unrelated to the variance in cognitive performance, suggesting that peripheral insulin and cerebral insulin resistance might play different roles in cognition, at least among people with type 2 diabetes [21].

Insulin dysregulation may affect the brain beyond alterations in glucose metabolism. Insulin is a potent neuromodulator [22], able to potentiate the NMDA, AMPA, and GABA receptors

that are important mediators of synaptic plasticity [23]. Also, Insulin-receptors are preponderantly present in areas of the brain implicated in cognition [24], participating in several important processes underlying cognitive functioning, such as neuronal survival and firing [25]. However, the mechanisms that may be activated when there are peripheral – out of the brain – abnormalities of insulin levels remain unclear. Most of the available insulin in the brain is derived from circulating blood levels, and there is little *de novo* synthesis in the brain [26]. Insulin crosses the brain-blood barrier using active transporters that are saturable [27, 28], and the binding of insulin to the receptors can also be modulated by a wide array of factors, for example, as bacterial infections increase their uptake [29], while steroids decrease it [30]. In parallel with AD, reduced insulin sensitivity, as well as decreased density of insulin receptors in the brain, has been reported to be associated with increased accumulation of Aβ and tau protein hyperphosphorylation [31, 32].

In AD patients, the concentrations of insulin in the CSF are decreased, while they are raised in the blood plasma, and this is more evident in the advanced stages of AD and patients without APOE-4 allele [33]. Concurrently, there are other abnormalities that may or may not be related to cerebral insulin alterations. Several experimental pieces of evidence support the link between AD and type 2 diabetes through mitochondrial alterations and oxidative stress, altered energy and glucose metabolism, cholesterol modifications, and dysfunctional protein O-GlcNAcylation [22].

Alzheimer's Disease Biomarkers in or at High Risk of Diabetes

Imaging and biomarker studies in humans are just beginning to provide insight into how diabetes and prediabetes may influence the progression of Alzheimer's disease. Insulin resistance does not appear to influence CSF AD-related biomarkers (amyloid β-peptide (Aβ), total tau and tau phosphorylated at the Thr181 epitope) in cognitively healthy individuals [34]. However, in the same study, a significant relationship was reported between continuous values of plasma insulin and CSF Aβ/tau, driven by the correlation between insulin levels and levels of tau protein, and thus suggesting a link between insulin resistance and neuronal degeneration. This finding is not surprising, as studies in animal models have demonstrated an association between hyperinsulinemia and tau pathology [35]. Imaging studies assessing the accumulation of AD biomarkers in the brain tissue in humans are scarce. TAUPET is an ongoing study (NCT03024944) assessing whether diabetes status type 2 diabetes and pre-diabetes, compared with normal glucose tolerance, is associated with increased tau accumulation in the brain of a community-based group of middle-aged Caribbean-Hispanics. Similar strategies will provide clarification as to the effect of insulin resistance in the progression of the neurodegenerative and vascular changes associated with AD.

Emerging Therapeutic Approaches

Advances in the knowledge of AD and type 2 diabetes have encouraged the development of treatments for preventing the pathogenic events that lead to severe cognitive impairment in individuals with prediabetes, metabolic syndrome or diabetes (Table 1), focused mainly on reducing brain insulin resistance. Clinical trials were identified using the public website

www.clinicaltrials.gov, which has tracked clinical trials since 2007. On May 1, 2017, there were twelve registered studies with the goal of either preventing the progression of MCI to AD, preventing MCI in people with or at high risk of type 2 diabetes and nine of them were ongoing. The studies are being carried out in four countries, and only two of them have concluded at the time of writing this review.

Glucagon-Like Peptide 1 (GLP1)

Glucagon-like peptide 1 (GLP1) agonists have been shown to offer neuroprotection [36], reverse brain insulin resistance [37, 38], reduce amyloid-β peptide accumulation and cytotoxicity [39], and decrease tau hyper-phosphorylation [40] in cellular and animal models of AD. Exenatide is one of the GLP-1 agonists that has been shown to decrease insulin resistance in the brain [37] and has already demonstrated clinical effectiveness to improve cognitive performance in patients with Parkinson's disease [41]. The purpose of the clinical trial using Exetanide NCT01255163 was to prevent/slow the progression of cognitive dysfunction and related biomarkers in dysglycemic/prediabetic patients with MCI. The intervention consisted of subcutaneous injections of 2 mg long-acting exenatide once weekly.

Acetylcholinesterase inhibitors (AChEI)

The most widely used drugs for the symptomatic treatment of AD in clinical practice are AChEI. Besides its cholinergic effect, Galantamine has significant antiinflammatory effects [42], suppressing serum TNF and IL-6 levels, and decreasing body weight and abdominal adiposity and alleviating insulin resistance and fatty liver in mice with high-fat diet–induced obesity [43]. In AD, there is a significant state of neuroinflammation that contributes to the neurodegenerative process, especially the activated microglia [44]. The clinical trial NCT02283242 was established with the purpose of investigating the effects of Galantamine on inflammatory markers, as well as on abdominal visceral and epicardial fat and oxidative stress in patients with metabolic syndrome. The intervention consisted of the oral use of Galantamine for 12 weeks (8 mg for four weeks and 16 mg for eight weeks).

Vitamin D3 - Cholecalciferol

Meta-analyses of cross-sectional studies have reported impaired cognitive function among individuals with insufficient levels of Vitamin D [45], while analyses of longitudinal studies revealed a nearly two-fold risk of incident cognitive impairment [46] and a 20% increased risk of developing AD [47]. However, clinical interventional studies have failed to show that supplementation with Vitamin D improves cognitive outcomes in individuals [48]. The purposes of the clinical trial NCT02416193 were to determine (1) the effect of vitamin D3 supplementation on cognitive function and (2) the effect of vitamin D3 supplementation on diabetes self-management in participants with type 2 diabetes who have symptoms of cognitive impairment but are not demented.

Resveratrol

Resveratrol is a potent caloric restriction-mimetic, able to penetrate the brain-blood barrier and showing positive influence on human cerebral blood flow [49], glucose control [50] and

verbal episodic memory performance [51]. It is found in grapes, red wine, peanuts and certain berries. The vast majority of studies dealing with the biological activity of resveratrol have been carried out *in vitro* and, to a lesser extent, in animal models [52]. Relatively few human clinical trials have been performed so far, and the main obstacle to translating the output of *in vitro* studies using resveratrol on humans relies on rapid metabolization, and consequentially, low bioavailability of the molecule [53].

Not only is there no clear dose-response concerning consumption of resveratrol and its metabolites, but in the brain, the availability or lack thereof of any of these metabolites is even lower than in blood [53]. Furthermore, the dose required to maximize effects without safety concerns is not yet known, and it is uncertain whether chronic ingestion of low resveratrol doses can exert more benefits than short-time exposures to high resveratrol doses [52].

In animal models, resveratrol influences the levels of several inflammatory response markers found to be elevated in diabetes, and other chronic disorders [54–56]. In humans, conflicting results [57, 58] and the lack of confirmation of several mechanisms involved in its activity in 'preclinical' models [52] preclude its current pharmacological use in patients with or at high risk of diabetes, or at high risk for development of cognitive impairment. However, recent clinical trials support the notion that resveratrol is capable of increasing cerebral blood flow during task performance [59, 49, 60] and enhancing oxygen extraction [49], reducing glycated hemoglobin A1c, preserving hippocampus volume, and improving hippocampus resting state functional connectivity in at-risk patients for dementia [61]. A randomized, double-blind clinical trial phase 1 (NCT02502253) will evaluate the effects of a Bioactive Dietary Polyphenol Preparation (BDPP), a combination of two nutraceutical preparations (grape seed polyphenolic extract, and resveratrol) in mood and cognition of patients with MCI and prediabetes or type 2 diabetes.

Improved Control of Vascular Risk Factors

A growing body of evidence indicates that potentially modi able cardiovascular risk factors may play an important role in the high prevalence of AD, as well as in type 2 diabetes [62]. The Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability (FINGER) [63] – a 2 year multidomain intervention of diet, exercise, cognitive training, and vascular risk monitoring versus control to prevent cognitive decline in at-risk elderly people – found that there were significant intervention effects on the primary outcome (overall cognition), main cognitive secondary outcomes (executive functioning and processing speed), and other secondary outcomes (body mass index, dietary habits, and physical activity). However, it has not been clearly determined whether these vascular factors also affect AD progression itself and thus whether controlling vascular conditions can slow this progression [64]. Some studies show that there is a lower conversion rate from MCI to dementia, and lower progression of AD in patients in whom all vascular risk factors were treated compared to those in whom only some of the risk factors were treated [65, 66]. However other studies show no clinical impact [67] or improvement of cognition in overweight or obese patients with type 2 diabetes [68].

The COVARAD is an ongoing clinical trial (NCT01423396) that compares the effect of "optimal" vs. "standard" care of hypertension, diabetes and dyslipidemia in AD patients, with the underlying hypothesis that those with stricter control of the risk factors will exhibit a slower cognitive decline. The BFIT is another clinical trial (NCT03117829) that compares cerebral blood flow, cognitive measures, and metabolomics markers in 40 sedentary (exercise <1 hour/week) participants who are 45–65 years of age, have impaired fasting glucose and are cognitively normal, and that undergo a 12-week diet and exercise intervention.

Dietary Pattern

Changes to diet have been recognized as a promising target for prevention of cognitive decline and AD [69, 70]. However, the optimal diet necessary to prevent the development of Alzheimer's disease and the progression of cognitive decline has yet to be identified, particularly when the exposure to nutritional patterns has occurred for several decades and the individual may already be suffering from obesity, dyslipidemia, and/or diabetes. It is less problematic to study naturally occurring dietary patterns that are associated with fewer of these consequences, including dementia. Indeed, this approach has allowed the identification of the Mediterranean dietary pattern has been linked most consistently to lower Alzheimer's disease incidence [71], and a Japanese pattern consisting of a high intake of fish, fruits and vegetables, potatoes, mushrooms, seaweeds, pickles, and soybeans that were also related to a lower risk of dementia [72]. At the same time, adverse dietary patterns have been identified. For example, a pro-inflammatory dietary pattern characterized by higher intake of red meat, processed meat, peas and legumes, and fried food, and lower intake of whole grains was found to be associated with higher inflammatory markers and accelerated cognitive decline at older ages [73]. The ongoing BEAM study (NCT02984540) compares the effects of a low-carbohydrate diet and a low fat diet for adults with mild memory loss and adults with pre-diabetes. The data collected will help determine changes in cognitive function, brain structure and function, and levels of certain proteins and hormones in body fluids.

Diets containing a preponderance of low-glycemic index food, i.e. containing carbohydrates leading to a slower release of glucose (e.g., rye bread) [74], low in saturated fats [75] and low in sodium [76], have been found to be associated with less cognitive impairment in old age. However, there is little consensus about recommendations, because of conflicting results and lack of randomized control trials. The MEAL-2 study (NCT02463084) was designed to compare the effects of a one-month diet high in saturated fat, glycemic index, and salt, to a diet low in these nutritional parameters on memory and other cognitive functions, magnetic resonance imaging measures of brain structure, function, and perfusion, as well as on blood and cerebrospinal fluid levels of amyloid-beta (Aβ), insulin, lipids cytokines, apolipoprotein E, apolipoprotein J, cortisol, soluble low density lipoprotein receptor-related protein, and glucose, in middle-aged adults (45–65 years of age) with normal cognition or mild cognitive impairment and prediabetes.

Meal frequency and timing, and calorie content of the diet have been suggested as potential modulators and influencers of disease trajectory during lifecourse [77, 78]. Diets that include calorie restriction and fasting have been associated with improved cognitive

performance, but few randomized clinical trials have been performed. A randomized controlled trial (NCT02460783) was established to test the effect of calorie restriction – defined as 500–600 calories a day for two consecutive days, followed by non-restricted eating for 5 days (5–2 CR) – on memory and executive function, resting state default mode network activity, brain metabolism, and AD biomarkers, in overweight to obese women and men (between 55 and 70 years of age.

Conclusions

Evidence suggests that patients with type 2 diabetes are at an increased risk of developing AD and that insulin resistance can lead to cognitive impairment [16, 79] Because both conditions are increasing exponentially, and only palliative treatments exist; new therapeutic targets for prevention, treatment and reversal of the decline in cognition are needed urgently. Intensive research efforts in preclinical models have provided numerous hypotheses about the interaction between insulin resistance and neurodegeneration through a plethora of pathways. There is not enough evidence to provide specific recommendations to prevent the cognitive decline in individuals with or at high risk of type 2 diabetes [80].

Approximately 60% of elderly adults with diabetes have at least one comorbid chronic disease [81], and as many as 40% of them have four or more comorbid diseases [82]. Early diagnosis of cognitive impairment and the identification of the subset of patients at a higher risk of developing AD is a challenge for healthcare providers. Most of the diabetes care guidelines typically focus on decreasing diabetes-related microvascular and cardiovascular complications, as well the prevention of hypoglycemia, as strategies to account for cognitive dysfunction in the tailoring of glycemic therapy, and do not suggest specific diets, exercise routines, or pharmacological agents [83]. Several ongoing trials are attempting to identify the usefulness of several compounds, as well as lifestyle changes including exercise and diet.

Acknowledgments

Abbreviations

Aβ	Amyloid β-peptide
AChEI	Acetylcholinesterase inhibitors
AD	Alzheimer's Disease
AMPA	α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid
APOE	Apolipoprotein E
BDPP	Bioactive Dietary Polyphenol Preparation

CSF	Cerebral Spinal Fluid
GABA	gamma-aminobutyric acid
GLP1	Glucagon-Like Peptide 1
HOMA2-IR	Homeostasis Model Assessment of Insulin Resistance
IL-6	Interleukine 6
MCI	Mild Cognitive Impairment
NMDA	*N*-methyl-D-aspartate
TNF	Tumor Necrosis Factor

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Table 1

Interventions for Cognitive Decline in Patients with or at Risk of Type 2

Study	Participants	Intervention	ClinicalTrials.gov Identifier	Country	Completion
Impact of Controlling Vascular Risk Factors on the Progression of Alzheimer's Disease (COVARAD)	Diabetes Type 2, Hypertension or Dyslipidemia	Optimal care for vascular risk factors	NCT01423396	France	2020
Diet and Exercise Study to Improve Brain Blood Flow: Blood Flow Improvement Trial (BFIT)	Pre-diabetes	Diet and exercise	NCT03117829	United States	2018
BDPP Treatment for Mild Cognitive Impairment (MCI) and Prediabetes or Type 2 Diabetes Mellitus (BDPP)	Diabetes Type 2 Pre-Diabetes	Resveratrol	NCT02502253	United States	2018
Effect of a Modified Ketogenic- Mediterranean Diet on Alzheimer's Disease (BEAM)	Pre-diabetes	Low- Carbohydrate vs Low-Fat Diet	NCT02984540	United States	2018
Can Vitamin D3 Improve Cognitive Function in Individuals With Type 2 Diabetes? (THINK-D)	Diabetes Type 2	Cholecalciferol	NCT02416193	United States	2018
Intermittent Calorie Restriction, Insulin Resistance, and Biomarkers of Brain Function	Overweight or Obese	Intermittent dietary restriction	NCT02460783	United States	2017
Galantamine Effects in Patients With Metabolic Syndrome (GALANTA-MS)	Metabolic Syndrome	Galantamine	NCT02283242	Brazil	2017
Long-acting Exenatide and Cognitive Decline in Dysglycemic Patients (DRINN)	Dysglycemia/Pre-diabetes	Exenatide	NCT02847403	Italy	2017
Macronutrient Effects on Alzheimer's Disease (MEAL-2 Diabetes	Pre-diabetes	Low vs High glycemic index Diet	NCT02463084	United States	2016